REMARKS

I. Claim Status

Claims 1-18 are currently pending. Claims 3-6, 8, 11, and 12 have been withdrawn from consideration. Claims 1, 2, 7, 9, 10, and 13-18 are rejected. No claims have been amended or added by this paper.

II. 35 U.S.C. § 103(a) Rejection

A. Claims 1, 2, 7, 9, 10, 13-15, 17, and 18

Claims 1, 2, 7, 9, 10, 13-15, 17, and 18 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Nos. 5,902,807 ("Haapalinna") and 5,492,907 ("Pickar") in view of Parwani, A. et al., "Impaired Prepulse Inhibition of Acoustic Startle in Schizophrenia," *Biol. Psych.* (2000) 47:662-669 ("Parwani"). Office Action dated October 28, 2009, page 6 ("Office Action"). Applicants respectfully disagree with and traverse this rejection.

As an initial matter, Applicants note that claims 17 and 18 depend from independent claim 16, which was not rejected as obvious over the combination of Haapalinna, Pickar, and Parawani. Accordingly, Applicants respectfully submit that the rejections of claims 17 and 18 are in error.

A *prima facie* case of obviousness has not been established because one of ordinary skill in the art would have been led away from combining the teachings of Haapalinna and Pickar, and Applicants' unexpected and superior results over non-selective alpha-2-adrenoceptor antagonists supports the non-obviousness of the instant claims.

The Office states that "Applicants argue that Pickar's [*sic*] teaches away from the instant claims," (Office Action, page 5) but that was not and is not Applicants' position. Instead, Applicants, as asserted in their June 18, 2009, Amendment, contend that a skilled artisan would not have been motivated to combine Haapalinna and Pickar.

A *prima facie* case of obviousness cannot be established where the references teach away from their combination, as in the present case. M.P.E.P. § 2145(X)(D)(2); *see also In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (holding that the combination of references was improper where one taught the interchangeability of antimony and an alkali metal and the other expressly excluded antimony).

As thoroughly explained in Applicants' June 18, 2009, Amendment, a skilled artisan would not have been led to combine Haapalinna, which discloses methods of treating ***stress-induced mental disorders*** with ***selective*** alpha-2C-adrenoceptors antagonists, with Pickar, which discloses methods of treatment for ***schizophrenia and other psychotic illnesses*** with ***non-selective*** alpha-adrenoceptor antagonists in combination with D_2 dopamine receptor antagonists. Not only does Haapalinna teach away from its combination with Pickar, it also undermines any reasonable expectation of success one of ordinary skill in the art might have had in substituting alpha-2C-adrenoceptor antagonists into Pickar's methods.

Haapalinna discloses methods for the treatment of stress-induced mental illnesses, such as anxiety and post-traumatic stress disorder, (col. 2, lines 37-44) using antagonists that have "a ten-fold preference to the alpha-2C subtype over the other alpha-2-subtypes." Haapalinna, col. 3, lines 8-9. In contrast, Pickar discloses that idazoxan, a non-specific alpha-2-adrenoceptor antagonist (Haapalinna, col. 1, lines 25-

28) is a particularly preferred embodiment (col. 2, lines 64-67) and is, in fact, the only alpha-2 adrenoceptor antagonist used in Pickar's examples (Examples 1 and 2). Haapalinna's unfavorable comparison of non-selective antagonists, like those disclosed in Pickar, to alpha-2C-adrenoceptor antagonists would have discouraged one of ordinary skill in the art from the combination proposed by Office.

In fact, Haapalinna states that non-specific alpha-2-adrenoceptor antagonists actually **cause anxiety**, one of the very conditions that Haapalinna seeks to treat. Haapalinna, col. 1, lines 18-19 ("Conventionally antagonists of alpha-2-adrenoceptors, such as yohimbine, have been found to anxiogenic [i.e., anxiety producing].") Furthermore, the non-selective alpha-2-adrenoceptor antagonists showed either no or little effect when compared to alpha-2C-adrenoceptor antagonists in tests in Haapalinna. In particular, the non-selective antagonists—in contrast to the alpha-2C selective antagonists—1) did not prevent the propagation of stress-induced behavioral despair (col. 6, lines 1-6); 2) "did not provide any anxiolytic [i.e., anxiety reducing] response" (col. 7, lines 14-19); and 3) potentiated neophobic stress (col. 7, lines 44-49). Thus, the results of Haapalinna's experiments expressly teach away from the interchangeability of selective and non-selective alpha-2-adrenoceptors to treat, in particular, stress-induced disorders.

Moreover, a skilled artisan would not have been led to combine Haapalinna and Pickar for the additional reason that mental illnesses, contrary to the Office's contention (Office Action, page 8),[1] are not all the same. Indeed, different mental illnesses can

[1] Applicants respectfully point out again that Haapalinna does not disclose that alpha-2C antagonists treat mental illness broadly. As noted before, Haapalinna discloses that (continued...)

have very different etiologies and mechanisms of action. And the skilled artisan would have known that the non-selective alpha-2-adrenoceptors of Pickar were not necessarily affecting the sensorimotor gating defects in schizophrenic patients because schizophrenia and the other psychotic illnesses disclosed in Pickar result from many interconnected physiochemical imbalances, not only from sensorimotor gating defects. Indeed, Applicants' own specification shows that the non-specific antagonists of Pickar likely were not affecting the sensorimotor gating deficiencies because atipamezole, a non-specific alpha-2-adrenoceptor antagonist, not only significantly increased the startle reactivity in the mouse model, it also had no effect on the PPI phenomenon. Specification, page 5, lines 3-11, and Figures 2A and 2B. Therefore, for the additional reason that not all mental illnesses are equal or treated by the same medicaments, a skilled artisan would not have been led to combine the teachings from a document that discusses stress-induced illnesses such as anxiety with the teachings of a documents that discusses psychotic illnesses such as schizophrenia.

Parwani, on which the Office relies for the teaching "that schizophrenic patients are known for having reduced sensorimotor gating," does not make up for the conflicting teachings of Haapalinna and Pickar.

And finally, Applicants have shown that an exemplary alpha-2C-adrenoceptor antagonist is significantly better than a non-selective antagonist. Sensorimotor gating deficiencies can be observed by a decreased prepulse inhibition (PPI) attributed to sensory flooding and cognitive fragmentation. Parwani, page 662. In other words,

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(...continued)
alpha-2C adrenoceptor antagonists are useful to treat stress-induced mental illnesses and not all mental illnesses, in general.

patients with sensorimotor gating defects are unable to shut out trivial sensory stimulation and are surprised by a startling event even when a pre-pulse, a.k.a. warning, is given. Applicants' presently claimed inventions increase this PPI inhibition, e.g., help to eliminate sensory flooding, using alpha-2C-adrenoceptor antagonists. One such exemplary alpha-2C anatagonist was shown to dose dependently and significantly increase PPI. Specification, page 5, lines 3-7, page 3, lines 19-27, and Figure 2B. In stark contrast, a non-selective alpha-2 antagonist not only increased the startle reflex *per se*, it also showed no effect on PPI in the mouse model. Specification, page 5 lines 7-11, page 3, lines 19-27, and Figures 2A and 2B. Applicants' results bolster the non-obviousness of the instant inventions.

For the reasons of record and the reasons presented above, the Office has not established a *prima facie* case of obviousness. As a result, this rejection should be withdrawn.

B. Claim 16

Claim 16 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Haapalinna, Pickar, and Parwani, as applied to claims 1, 2, 7, 9-10 and 13-15, 17-18 above, and further in view of U.S. Patent No. 6,593,324 ("Wurster"). Office Action, page 8. Applicants respectfully disagree with and traverse this rejection.

Haapalinna, Pickar, and Parwani are discussed above. The Office admits that "[n]one of cited references expressly teach[es] acridin-9-yl-[4-(4-methylpiperazin-1- yl)-phenylamine." *Id.*

However, the Office asserts that Wurster discloses the claimed compound and a method of treating schizophrenia with an alpha-2 adrenoceptors (claim 16). Office Action, page 9.[2] The Office concludes that

> [i]t would have been obvious to one of ordinary skills in the art to employ acridin-9-yl-[4-(4-methylpiperazin-1- yl)-phenylamine for the treatment of schizophrenia and sensorimotor gating deficits as taught by Parwani and Wurster. One would have been motivated to employ acridin-9-yl-[4-(4-methylpiperazin-1- yl)-phenylamine for the treatment of schizophrenia and sensorimotor gating deficits because it is known in the art that alpha-2 adrenoceptors are effective in the treatment of schizophrenia and sensorimotor gating deficits often associated with schizophrenia as taught by Wurster.

Although Wurster discloses that its compounds, including acridin-9-yl-[4-(4-methylpiperazin-1- yl)-phenylamine, may be used to treat schizophrenia (col. 24, lines 30 and 39-40), Wurster fails to compensate for the deficiencies of Haapalinna, Pickar, and Parwani, as discussed above. Even though Wurster discloses that an alpha-2C-adrenoceptor antagonist may be used to treat schizophrenia, it—like the other cited art—is wholly silent with respect to whether alpha-2C antagonists may be able to ameliorate sensorimotor gating deficits, such as recited by the present claims. And, one of ordinary skill in the art would not have been able to infer such activity because Wurster discloses that its compounds can be used to treat many different conditions (col. 24, lines 32-53), some of which are not even CNS disorders, let alone tied to sensorimotor gating defects. Thus, a skilled artisan would not have been motivated to use the compounds of Wurster "for [treating] at least one symptom of a disorder or condition associated with sensorimotor gating deficits."

[2] The Office cites claim 15, but claim 16 is the claim that recites acridin-9-yl-[4-(4-methylpiperazin-1- yl)-phenylamine.

That sensorimotor gating defects were known to be present in schizophrenic patients (Parwani) has no bearing on the fact that it was not known, at the time of invention, that alpha-2C antagonists had beneficial action on sensorimotor gating deficits. As a result, a *prima facie* case of obviousness has not been established because "obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." M.P.E.P. § 2141.02(V) (citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d (BNA) 1955, 1957 (Fed. Cir. 1993)). For at least this reason, this rejection should be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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